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TITLE PAGE

Contradictory Advice for People Who Inject Drugs in the 2016 EASL Recommendations on Treatment of Hepatitis C

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FOOTNOTE PAGE

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The 2016 EASL Recommendations on Treatment of Hepatitis C provide important international guidance for the clinical management of HCV infection. The guidance is particularly crucial in the current environment of rapidly changing direct-acting antiviral (DAA) therapeutics. However, there are inherent contradictions within the EASL Recommendations for people who inject drugs (PWID). The EASL Recommendations state that "Treatment should be considered without delay in individuals at risk of transmitting HCV (e.g. active injection drug users)", given the potential for preventing onward HCV transmission and reductions in HCV prevalence at a population-level. Such prioritization is in keeping with guidelines from AASLD/IDSA, the World Health Organization, and strongly supported by the International Network for Hepatitis in Substance Users (INHSU). Yet, the EASL Recommendations present prescriptive and rigid guidance, including that PWID should "accept to undergo integrated management of their substance use, including syringe exchange program, substitution therapy and other general harm reduction strategies" prior to receiving DAA therapy and that "HCV treatment for PWID should be considered on an individualized basis and delivered within a multidisciplinary team setting." Although appropriate drug dependency management and multidisciplinary care are important aspects of provision of care for PWID, the indication that they are essential is reflective of the interferon-containing era, is restrictive, and non-evidence based.

While engagement in needle/syringe programs, OST, and other drug treatments are important components for improving drug user health and should be encouraged, these should not be requirements for HCV therapy. Further, some cocaine and/or methamphetamine injectors may not be opioid dependent and not eligible to receive OST, and some people who use opioids may not want or need OST.

In the DAA era, HCV treatment should be considered for all PWID. There are no data to support statements within the recommendations that "Drug and alcohol users or any other patients with on-going social issues and/or history of psychiatric disease, and those with more frequent drug use during therapy, are at risk of lower adherence and reduced likelihood of achieving SVR." and that "They need to be monitored more closely during therapy and need more intensive multidisciplinary support". While DAA therapy should be individualized based on the patient, many PWID may not require regular clinic visits and multidisciplinary support.

The 2016 EASL recommendations also do not distinguish between people who injected drugs at some point in their lifetime and have ceased injecting ("former PWID") and people who have injected recently ("recent PWID", with definitions vary from 1-12 months). Among former PWID, there exists a population of people receiving OST, some of whom may be "recent PWID". Phase 3 clinical trials often include "former PWID" and people on OST (with no recent drug use), but almost always exclude recent PWID (including those receiving OST with recent drug use).

Among people receiving OST with no recent illicit drug use, post-hoc analyses of phase II/III trials of DAA therapy have demonstrated that treatment completion, adherence, and SVR12 are similar to those not receiving OST [1-6]. These trials only provide clinical guidance for HCV management among people receiving stable OST with no recent drug use.

Data on DAA treatment outcomes among people receiving OST with recent illicit drug use are now available from the Co-STAR study [7]. Treatment-naïve individuals with HCV genotype 1/4/6 infection receiving "stable" OST ($\geq$80% adherence to OST appointments in

the last three months) were enrolled (recent drug use did not exclude study participation) and treated with elbasvir/grazoprevir for 12 weeks. Overall, 96% completed therapy, >96.5% of participants demonstrated >95% adherence and SVR12 was 91% [7], comparable to trials in non-users. Importantly, drug use at baseline (62% all, 47% non-cannabinoids) and during treatment (60% all, 47% non-cannabinoids) did not impact SVR [7]. These data provide strong support for the efficacy and safety of DAA therapy in people receiving stable OST, including those with recent drug use.

Among people with recent illicit drug use (including those not receiving OST), real-world data on DAA treatment outcomes is emerging, with responses ranging from 95-98% [8, 9]. However, it is not clear from these studies as to the proportion of people with recent injecting. Future studies on HCV treatment among recent PWID should clearly define the study population and injecting drug use characteristics. There are several ongoing international studies evaluating DAA HCV regimens among people with recent injecting drug use, including SIMPLIFY (sofosbuvir/velpatasvir for 12 weeks; clinicaltrial.gov:NCT02336139) and HERO (randomized trial of directly observed sofosbuvir/velpatasvir therapy versus patient navigation; clinicaltrial.gov:NCT02824640). Although further data (clinical trial and "real-world") are needed to guide clinical management among people with recent injecting drug use, DAA HCV treatment should not be withheld from PWID with recent illicit drug use.

We strongly recommend that all PWID are considered for DAA therapy, for the individual-level benefits that therapeutic cure brings, with potential population-level benefits on HCV transmission further justification for prioritization.

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